

# The Relationship of Blood Lead Levels to Blood Pressure in the U.S. Population

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Numerous observations have indicated a relationship between moderate or heavy lead exposure and high blood pressure. To determine whether low-level lead exposure is related to blood pressure in the U.S. population, we analyzed data from the National Health and Nutrition Examination Survey II for persons 12 to 74 years of age. Significant correlations were found between blood lead and blood pressure for each race-gender group, and blood lead levels were significantly higher in groups with high diastolic blood pressure ( $> 90$  mm Hg). Multiple stepwise regression models were developed to predict blood pressure. After adjusting for age, race, and body mass index, blood lead levels were significantly related to systolic and diastolic pressures in males but not in females. These findings and those from other studies confirm the relationship of blood lead and blood pressure at relatively low levels commonly observed in the general population. The strength and importance of this relationship require further study through epidemiologic and metabolic investigations.

Numerous observations over many years have associated lead exposure with human disease (1,2). Since 1881, the cardiovascular system has been a focus of investigations about the toxic effects of lead (3-5). With moderate to heavy exposures, there have been studies reporting cerebrovascular disease and nephritis resulting in increased mortality (6,7). Moreover, toxic effects of lead on the kidney have been associated with the development of hypertension and its complications (5). These reports of toxicity have been related primarily to relatively high burdens of lead from occupational exposure, contaminated or adulterated alcohol, or deliberate poisoning. The issue of toxicity to the cardiovascular system at relatively low levels of blood lead exposure remained problematic until recently (3-12).

As data have become available on more general populations, it has been recognized that significant levels of blood lead were measured in persons not heretofore believed to have significant lead exposure (13). Two sources of lead exposure in adults have been proposed: contamination of air with fumes from leaded gasoline and soft water in contact with piping containing lead. For children, the consumption of leaded paint surfaces remains a major source even after wide prohibition of such paints.

For several years, we have been exploring blood pressure relationships using data from the U.S. national surveys, and the availability of data on blood lead in a sample of the U.S. population suggested that

exploration of this relationship in a general population would be useful (8,14). There were additional reasons to be interested in a lead-blood pressure relationship. Dietary calcium has been inversely related to blood pressure, and calcium intake has been observed to ameliorate the toxic effects of lead exposure (14-17). A considerable body of physiologic data has accumulated that indicate blood pressure increases in animals fed small amounts of lead at exposures similar to human environmental exposures (18,19). Based on the long historical association and the provocative findings of blood pressure effects at low levels of lead exposure, we analyzed data from the National Health and Nutrition Examination Survey II (NHANES II) to determine if an association existed between relatively low blood lead levels and blood pressure (8).

The details regarding survey design, sampling, and operation of NHANES II are described in detail elsewhere (20-22). This survey examined a national probability sample of the civilian noninstitutionalized U.S. population aged 6 months to 74 years. Blood lead was carefully measured in every other blood sample obtained from those 12 to 74 years (21). The analytical approach used the design and sampling biases that characterize this complex survey and are described elsewhere (22). In another presentation at this symposium, J. R. Landis provides another analytical scheme that considers operational aspects of the survey (23). These include the performance of the examinations over a 4-year period during which blood lead levels declined, and the mixture of urban/rural examination sites varied because of sampling.

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Several approaches were used to determine whether blood lead was related to blood pressure. First, adults were classified into blood pressure groups: normotensive ( $< 90$  mm Hg, diastolic), hypertensive ( $\geq 90$  mm Hg), or isolated systolic hypertensive ( $\geq 160$  mm Hg systolic and  $< 90$  mm Hg diastolic). The mean levels of blood lead were compared among these groups. Blood lead was found to be significantly higher for the groups with elevated diastolic pressures groups than for the normotensive or systolic hypertensive groups ( $p \leq 0.05$ ) (8). The differences were significant for men and women and for younger (21–55 years) and older (56–74 years) persons. This difference was present if treated hypertensive persons were included or excluded, indicating that the influence of lead on blood pressure was independent of medication. This analysis also provided evidence that dietary calcium intake was slightly but significantly lower in those who were classified as hypertensive (8).

To examine whether the relationship was linear, simple correlations were determined between blood pressure and blood lead. The natural logarithm of blood lead was used to provide a normal distribution of values. Simple regressions of blood lead on blood pressure yielded significant correlations for each race-gender group ranging between  $r = 0.11$  and  $r = 0.22$  ( $p < 0.001$ ).

The availability of data from a probability sample of the U.S. population covering a broad age range provides distributions of blood lead and blood pressure by age, race, and gender. The weighted mean blood lead (ln) is plotted for females 12 to 74 years in Figure 1 and for males 12 to 74 in Figure 2. Blood lead is generally higher for successively older age groups of males and females. Black men and women have higher blood lead levels than do white men and women although this

racial difference decreases at older ages (above 60 years). The levels of blood lead are lower for women than men at all ages and for both races as indicated by the different scales on the abscissa (Fig. 1). The distributions of mean blood pressure by age are similar to those for blood lead (Fig. 2), except for the male-female differences. Systolic blood pressure increases progressively for all race-gender groups, but diastolic pressure plateaus (for older white women and older black men) or declines (for older black women and older white men). Blood pressures for blacks are consistently higher than for whites at all ages over 25 years. Mean blood pressures for women are slightly greater than for men at older ages. These findings indicate that the age relationships for blood pressure and blood lead are similar by race and gender groups. Some of the effect of blood lead in analysis will be explained by adjustment for age because of this similarity.

Other relationships with blood lead were examined. The correlates for blood lead were developed using a regression model (Table 1). Separate regression models were developed for males and females as indicated by the two columns. The variance is explained ( $r^2$ ), and standardized regression coefficients are given for men and women in the table. Data from these complex national surveys can be analyzed without considering the survey design and sample biases, but often the findings differ. This is illustrated in these models by including coefficients that were significant in unweighted analysis but were not significant when sample weights were used. There are several interesting and significant correlations. Age was linearly related for men, but a quadratic term ( $\text{age}^2$ ) fit the data best for women. The population size where the respondent resided was directly correlated with blood lead levels for both men and women. This finding is

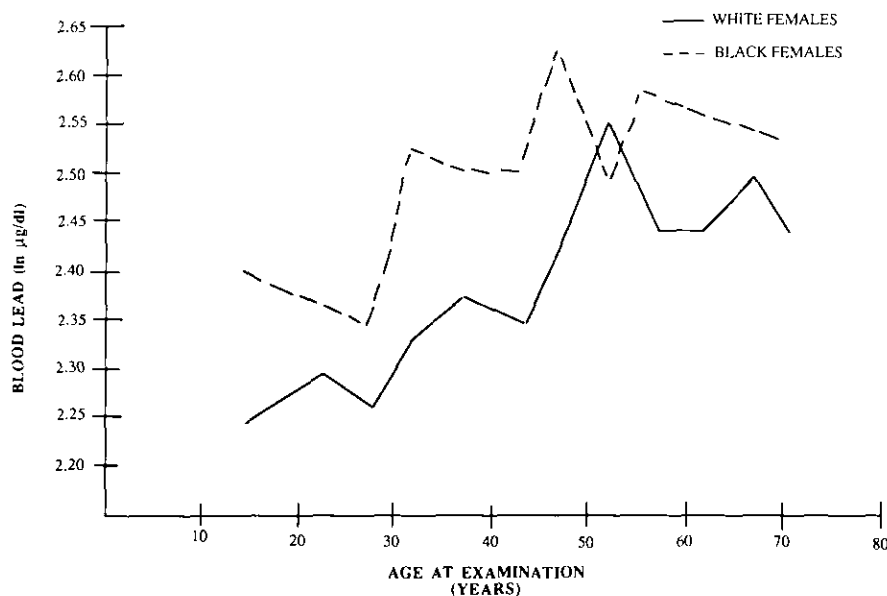


FIGURE 1. Mean blood lead levels (ln) by age for black and white females 12 to 74 years in U.S. population (1976–80). The levels generally are higher at successive older ages and higher for black males.

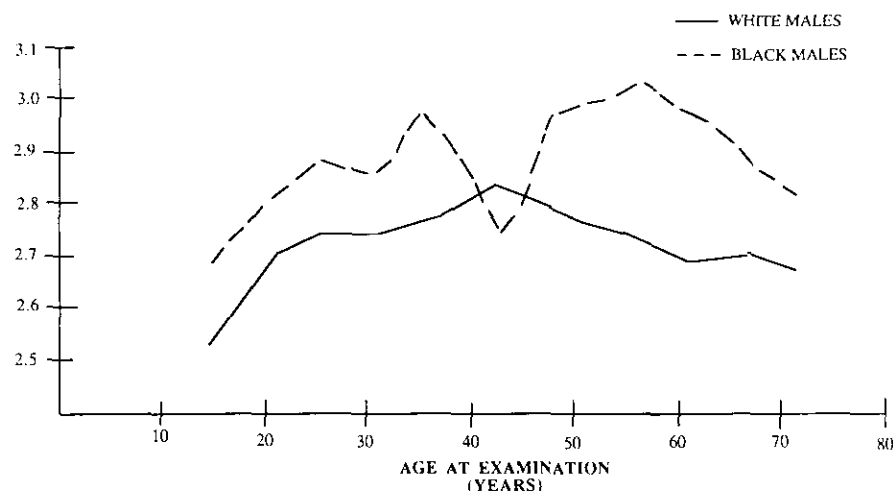


FIGURE 2. Mean blood lead levels (ln) by age for black and white males 12 to 74 years in the U.S. population (1976–80). Blood lead tends to be higher for older females and higher for black than white females.

Table 1. Standardized coefficients for blood lead (ln) regression models using sample weights.

Variables	Men	Women
$r^2$	0.180	0.191
$n$	2642	3161
Age <sup>2</sup>	(0.039) <sup>a</sup>	0.167
Age	0.171	0.002
Body mass index (weight/height <sup>2</sup> )	-0.034	-0.005
Population size	0.179	0.232
Smoking, packs/year	0.086	0.145
Alcohol, ounces/week	0.116	0.128
Red blood cell count	—	0.089
Hemoglobin	0.145	0.087
Vitamin C	-0.059	-0.066
Race (1—black)	0.065	0.073
SES (income-education)	-0.129	—
Serum copper	0.072	—
Dietary phosphorous	-0.065	—
Dietary calcium <sup>b</sup>	-0.033	-0.038
Dietary sodium <sup>b</sup>	-0.072	—
Dietary potassium <sup>b</sup>	—	0.036

<sup>a</sup>Numbers in parentheses indicate that statistically significant coefficients were selected in unweighted analysis but not when sample weights and design effects were used in analysis.

<sup>b</sup>From 24-hr recall dietary intake.

compatible with the finding that ambient lead, principally from automobile exhaust fumes from leaded gas, is the major current source of human lead exposure for the general population. Smoking (amount in packs per year) and alcohol consumption (ounces per week) have direct relationships to blood lead. Only two other variables had consistent associations in weighted analysis for both men and women. Hemoglobin concentration was directly related and vitamin C level was inversely related. Interestingly, dietary calcium assessed by 24-hr dietary recall was inversely related to blood lead, as might be expected from metabolic studies, but this association was not found when weighted analysis was done. This finding suggests that the sampling biases in the survey were related to blood lead. This survey over-

sampled older Americans, blacks, and those in the poverty category. Presumably, calcium intake was related to one or more of these oversampling biases, and, when the sampling weights were included, the relationship with calcium was lost. Parenthetically, this finding illustrates that sample weights should not be ignored in analyzing these survey data and that rather different results can be obtained whether or not the weights are used.

Multiple stepwise regression models were developed to predict blood pressure. The primary intent of these analyses was to develop the best-fitting model for blood pressure using independent variables that had been linked to blood pressure in previous studies. The selection of variables for these models was based on previous model development for blood pressure using data from these complex surveys (14). For example, age, body mass index (weight/height<sup>2</sup>) or skinfold thickness, race, and gender have been important predictors of blood pressure in all surveys and in numerous other large epidemiologic studies as well. Therefore, in developing these regression models, we entered age and body mass index as the first variable in the stepwise regression. Moreover, quadratic variables and interaction variables were developed and entered to achieve the best-fitting model (8). Separate models were developed for men and women and for systolic and diastolic pressure (Tables 2 and 3). The natural log of blood lead was used to normalize the distribution of values.

For males, blood lead contributes significantly to the variance of both systolic and diastolic pressure after adjusting for the effects of age, race, and body mass index (Table 2). The relationship is direct. By contrast, serum zinc has an inverse relationship, as might be expected from the competing metabolic effects of these elements. The finding of an independent effect for blood lead is more remarkable because of the similarity of blood lead and blood pressure distributions across age

**Table 2. Standardized regression coefficient for multiple regression models of blood pressures in males.**

Variable	Systolic	Diastolic
$r^2$	0.236	0.274
$n$	2823	2818
Age <sup>2</sup>	0.230	0.176
Age	0.100	-0.109
Quetelets	0.330	0.328
Age (blacks)	0.042	0.040
Race	—	0.070
Blood lead (ln scale)	0.061	0.049
Hemoglobin	0.074	0.114
Serum zinc	-0.046	-0.038

**Table 3. Standardized regression coefficient for multiple regression models of blood pressures in females.**

Variable	Systolic	Diastolic
$r^2$	0.363	0.269
$n$	2905	2897
Age <sup>2</sup>	0.430	0.212
Age	0.164	-0.039
Quetelets	0.290	0.356
Serum zinc	-0.058	-0.052
Red blood cell count	0.060	0.105
Dietary calcium	-0.039	-0.048
Alcohol, ounces/week	—	0.054

(Figs. 1, 2, and 3). One might have expected that adjusting for age would remove much of the variance attributable to blood lead levels. That it did not strengthens the importance of the relationship. Moreover, the variables entered into the regression model included those that were related to blood lead (Table 1), but none replaced blood lead and effectively maintained the variance. This provided a good test of the uniqueness of the relationship, as other related variables were given an opportunity to compete.

Blood lead did not enter the final regression model for blood pressure in women (Table 3). Serum zinc and dietary calcium were inversely related to systolic and

diastolic pressures. Alcohol ingestion and red blood cell count (RBC) were directly related to blood pressure and this was similar to the relationship found between these variables and blood lead. Additional steps in analysis suggested that alcohol, RBC, and dietary calcium competed for explanation of a similar portion of blood pressure variance as lead. When any two of these variables was excluded from the model, blood lead was selected as a significant predictor, but the predicted significant effect of lead on blood pressure. But how important is this effect of lead? In population studies of variance ( $r^2$ ) was not as great as the model presented in Table 3. The predicted variance of blood pressure in both models is somewhat greater than that achieved in other analyses of blood pressure using national data.

Subsequent analyses of this data set confined to white middle-aged men 40 to 59 years provided a more extensive test of the uniqueness of the blood lead contribution (9). In these analyses, almost all of the nutritional factors and blood biochemistries collected in NHANES II were included in the stepwise analysis after entry of age and body mass. Although some different nutritional variables were selected, the strength of the blood lead-blood pressure relationship was not affected by competition with this large array of variables.

These cross-sectional observations and several others provide evidence for an association between blood lead and blood pressure at levels that are observed in the general population (10-12). Moreover, there is an agreement between the human studies and animal studies regarding effects at low levels of lead exposure, and there are plausible biologic mechanisms for a lead effect. From these and other studies of population groups, there is general agreement for a statistically industrialized countries, the effects of excess weight, increasing age, and black race are consistently the most important predictors of blood pressure in adults. It has been difficult to demonstrate an effect of sodium for

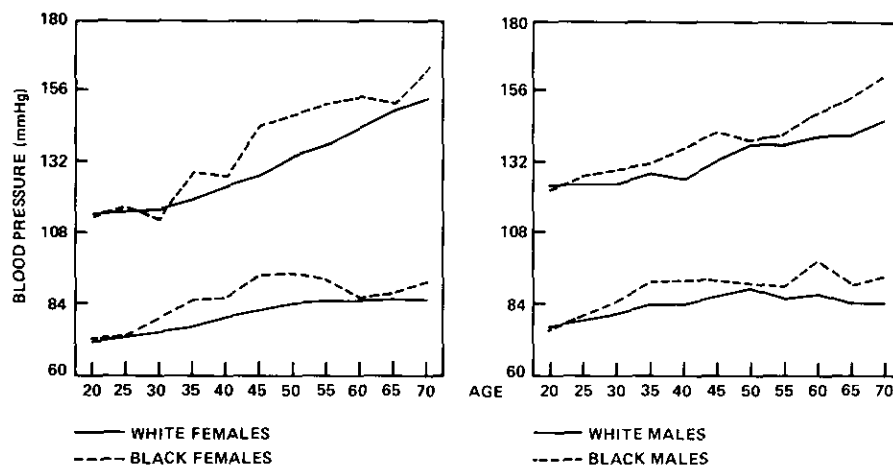


FIGURE 3. Mean systolic and diastolic blood pressures by age for females and males and females 20 to 74 years in U.S. population (1976-80). The panel on the left depicts black and white females and the panel on the right depicts black and white males. Note the similar patterns of blood pressure by age, race, and gender to those of blood lead levels in Figs. 1 and 2.

intrapopulation studies although cross-cultural and interpopulation studies suggest an effect. After adjusting for the effects of weight, age, and race, lead was the next most important predictor in men, and this effect was not diminished by trial of an array of nutritional and physiologic variables. The absolute effect of blood lead concentration on blood pressure could be estimated at 7 mm Hg systolic and 3 mm Hg diastolic between the levels of 14 and 30  $\mu\text{g}/\text{dL}$ , a range commonly found in the U.S. population. This estimate is in the range of the effect suggested in other studies (10,12) and somewhat greater than in another large study (11). While not large, this average effect is comparable to what is obtained on average from use of step one antihypertensive drugs. Moreover, a broad public impact on blood pressure could be anticipated from reduction of average blood lead levels. This potential reduction in blood lead levels can be estimated to have a sizable impact on cardiovascular events in the U.S. (9). Because of potential ameliorating effects of calcium and zinc intake, the balance of these elements and lead deserve attention.

There are additional analyses of existing data sets that might be useful. For example, the linkage between target organ damage and blood lead (and serum zinc) has been sought in NHANES II through evaluation of electrocardiographic changes. Blood lead directly (and serum zinc inversely) have been found to be related to left ventricular hypertrophy and Q-wave infarction (23). This affords a useful link between these trace metals and cardiovascular damage. Relationships could also be sought with echocardiographic or angiographic abnormalities. There are data from the Hispanic Health and Nutrition Examination Survey (HHANES) conducted from 1980 to 1984, and these data can be used to follow the changes in blood lead and blood pressure. Several large cohort studies of cardiovascular disease in young adults and in communities (CARDIA, ARIC) could include trace metal measurements and afford a longitudinal assessment of the effects of metals. These longitudinal observations would strengthen causal inferences. Finally, comparison of secular trends in the U.S. and in European and Asian countries would be of interest. Ambient lead levels are declining in countries banning leaded gasoline, but not in others, and it would be informative to contrast blood lead and blood pressure changes in countries with decreasing lead exposure with those having no change or a partial change. The implications for public policy and public health are important and the potential benefits compel further study.

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